Docket No. 65019-DC-PCT-US/JPW/AJM/NFM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Marc Feldmann and Ravinder N. Maini

Serial No. : Not Yet Known

Filed : Herewith

For : ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE TREATMENT OF TNF-MEDIATED DISEASE

1185 Avenue of the Americas
New York, New York 10036
August 3, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination, please make the following amendments to the above-identified application:

In the Specification

Please delete the paragraph on page 1, lines 5-15, and insert the following:

> This application is a continuation of U.S. Serial No. 08/690,775, filed August 1, 1996, which is a continuation-in-part of U.S. Serial No. 08/607,419, filed February 28, 1996, now abandoned, which is a continuation-in-part of PCT International Application No. PCT/GB94/00462, filed March 10, 1994, which is a continuation-in-part of U.S. Serial No. 08/403,785, now U.S. Patent No. 5,741,488, based on PCT

International Application No. PCT/GB93/02070, filed October 6, 1992, which is a continuation-in-part of U.S. Serial No. 07/958,248, filed October 8, 1992, now abandoned, the teachings of all of which are incorporated herein by reference.

In the Claims

Please cancel claims 1-31 without prejudice to applicants' right to pursue the subject matter of these claims in a continuing application.

Please add new claims 32-69 as follows:

32. (New) A method for treating or preventing a tumor necrosis factor-mediated disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts.

33. (New) The method of Claim 32, wherein said TNFα antagonist and methotrexate are administered simultaneously.

34. (New) The method of Claim 32, wherein said TNFα antagonist and methotrexate are administered sequentially.

35. (New) The method of Claim 32, wherein the tumor necrosis factor-mediated disease is selected from the group consisting of autoimmune disease, acute or chronic immune disease, inflammatory disease and neurodegenerative disease.

36. (New) The method of Claim 35, wherein said TNFα antagonist is administered in multiple doses.

37. (New) The method of Claim 32, wherein said TNFα antagonist prevents or inhibits TNFα synthesis or TNFα release.

38. (New) The method of Claim 37, wherein said TNFα antagonist is a phosphodiesterase inhibitor.

39. (New) The method of Claim 38, wherein said phosphodiesterase inhibitor is selected from the group consisting of pentoxifylline and rolipram.

40. (New) The method of Claim 37, wherein said TNFα antagonist is selected from the group consisting of thalidomide and tenidap.

41. (New) The method of Claim 38, wherein said TNFα antagonist is selected from the group consisting of an A2b adenosine receptor agonist and an A2b adenosine receptor enhancer.

42. (New) The method of Claim 36, wherein said TNFα antagonist is an anti-TNFα antibody or antigen-binding fragment thereof.

43. (New) The method of Claim 42, wherein said anti-TNFα antibody or antigen-binding fragment is a chimeric antibody or chimeric fragment, said chimeric antibody or chimeric fragment comprising a non-human variable region specific for TNFα or an antigen-binding portion thereof and a human

constant region.

44. (New) The method of Claim 43, wherein said chimeric antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

45. (New) The method of Claim 44, wherein said chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

46. (New) The method of Claim 44, wherein said chimeric antibody is monoclonal antibody cA2.

47. (New) The method of Claim 42, wherein said anti-TNFα antibody is a humanized antibody or antigen-binding fragment thereof.

48. (New) The method of Claim 47, wherein said humanized antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

49. (New) The method of Claim 42, wherein said anti-TNFα antibody is a resurfaced antibody or antigen-binding fragment thereof.

50. (New) The method of Claim 49, wherein said resurfaced antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.

51. (New) The method of Claim 36, wherein said TNFα antagonist is a soluble TNFα receptor or functional portion thereof.

52. (New) The method of Claim 51, wherein said soluble TNFα receptor is selected from the group consisting of p55 TNFα receptor and p75 TNFα receptor.

53. (New) The method of Claim 51, wherein said soluble TNFα receptor is a TNFα receptor multimeric molecule.

54. (New) The method of Claim 51, wherein said soluble TNFα receptor is a TNFα receptor immunoreceptor fusion molecule

55. (New) A method for treating or preventing arthritis in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts.

56. (New) The method of Claim 55, wherein said TNFα antagonist and methotrexate are administered simultaneously.

57. (New) The method of Claim 55, wherein said TNFα antagonist and methotrexate are administered sequentially.

58. (New) The method of Claim 55, wherein said TNFα antagonist is administered in multiple doses.

59. (New) The method of Claim 55, wherein said TNFα antagonist prevents or inhibits TNFα synthesis or TNFα release.

60. (New) A method for treating or preventing rheumatoid arthritis in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said

individual, in therapeutically effective amounts.

61. (New) The method of Claim 60, wherein said TNFα antagonist and methotrexate are administered simultaneously.

62. (New) The method of Claim 60, wherein said TNFα antagonist and methotrexate are administered sequentially.

63. (New) The method of Claim 60, wherein said TNFα antagonist is administered in multiple doses.

64. (New) The method of Claim 60, wherein said TNFα antagonist prevents or inhibits TNFα synthesis or TNFα release.

65. (New) A method for treating or preventing Crohn's disease in an individual in need thereof comprising co-administering methotrexate and a TNFα antagonist to said individual, in therapeutically effective amounts.

66. (New) The method of Claim 65, wherein said TNFα antagonist and methotrexate are administered simultaneously.

67. (New) The method of Claim 65, wherein said TNFα antagonist and methotrexate are administered sequentially.

68. (New) The method of Claim 65, wherein said TNFα antagonist is administered in multiple doses.

69. (New) The method of Claim 65, wherein said TNFα antagonist prevents or inhibits TNFα synthesis or TNFα release.

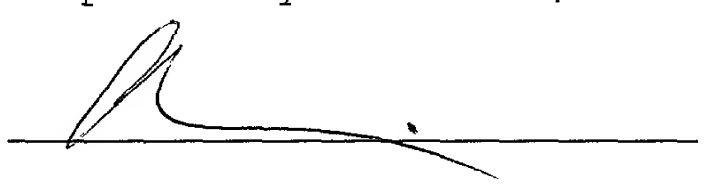
REMARKS

This application is a continuation of U.S. Serial No. 08/690,775, filed August 1, 1996. The '775 Application is due to issue as U.S. Patent No. 6,270,766 on August 7, 2001. Accordingly, the '775 application is pending today, and this continuation application is being timely filed.

By this Preliminary Amendment, applicants have amended the specification to incorporate a priority claim to parent application U.S. Serial No. 08/690,775. Applicants have also canceled claims 1-31 without prejudice and have added new claims 32-69 to introduce certain format changes. Accordingly new claims 32-69 are pending in the subject application.

No fee, other than the enclosed $1,114.00 application filing fee, is deemed necessary in connection with the filing of this Preliminary Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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